Background and Overview of the CIOMS VII Project: The DSUR

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DISCLAIMER (1)

The opinions expressed are my own, as a member of the CIOMS VII Working Group.

The opinions expressed are not necessarily those of the FDA.

DISCLAIMER (2)

CIOMS is a “think tank.”

CIOMS does not have any official (or unofficial) regulatory authority!

It influences and persuades through the strength of its ideas and by its credibility.

Current regulations pertain unless and until modified!

CIOMS Working Group VII

"The Development Safety Update Report (DSUR): A Harmonized Approach to Periodic Safety Update Reporting During Clinical Trials"

- AFSSAPS (France)
- BfARM, MOH (Germany)
- EMEA (EU)
- FDA (US)
- Health Canada
- MHRA (UK)
- PMDA (Japan)
- TGA (Australia)
- WHO (Geneva)

- Consultants (US, Japan)

- Bayer (Germany)
- Eisai (Japan)
- Eli Lilly (UK)
- GSK (UK)
- Merck (US)
- Novartis (Switzerland)
- Pfizer (Italy, US)
- Roche (US)
- Sanofi-aventis (France)
- Wyeth (US)

Pre-Approval Periodic Safety Reporting Requirements

- US - IND Annual Report

  21 CFR 312.33

- EU - Clinical Trials Directive (relatively new)

- Other countries (e.g., Switzerland)

CIOMS WG VI Recommendation: A Globally Harmonized "Development Safety Update Report"

- Harmonize US IND Annual Report and EU CT Directive's Annual Safety Report
- One annual report for all regulators
- Standard format, content, timing
- Extension of PSUR to pre-approval; convenient transition to the PSUR (consistent terminology and definitions for pre- and post-approval)
- International birth date (first authorization anywhere)
- IB section as reference safety document (or Development Core Safety Information [DCSI])

US IND Annual Report (AR) versus EU Annual Safety Report (ASR): Some Differences (1)

	IND AR	ASR
purpose	progress report	benefit-risk assessment
timing	IND anniversary date	Date of 1st authorization of a clinical trial of IMP by authority in member state
frequency	annual	annual, or on request

US IND Annual Report (AR) versus EU Annual Safety Report (ASR): Some Differences (2)

	IND AR	ASR
recipients	FDA	EMEA, Member States, Ethics Committees
content	study data and summary information	benefit-risk assessment; supporting tables
feedback by regulators	may be requested	not mentioned

US IND Annual Report (AR) versus EU Annual Safety Report (ASR): Some Differences (3)

	IND AR	ASR
short term trials	end of study report for all trials within 1 year of end	safety report within 90 days
adverse events included	all serious ± associated ± expected	SUSARs; serious, associated; ± expected

US IND Annual Report (AR) versus EU Annual Safety Report (ASR): Some Differences (4)

	IND AR	ASR
Format and Summary Content	Tabular summary of most frequent and most serious AEs by body system. Summary of all IND expedited reports for the period. Lists of deaths (w/ cause) and dropouts. List of completed non-clinical studies and result summary.	Concise global analysis; benefit-risk evaluation; implications for trial subjects; proposed measures to minimize risk; rationale for updates of study documents and procedures; supporting results of non-clinical studies; other considerations

US IND Annual Report (AR) versus EU Annual Safety Report (ASR): Some Differences (5)

	IND AR
Other	• Description of the general investigational plan for the coming year • Description of IB revisions, new IB • Description of significant Phase 1 protocol modifications • Summary of significant foreign marketing developments during past year • Log of any outstanding IND business

General Purpose and Scope of the DSUR

- All pertinent, new, safety-related information, clinical and non-clinical, since the most recent report
- Cumulative and interval summary of key safety findings
- Relate clinical safety data to patient exposure
- Market authorization information; significant variations related to safety
- Summary of emerging and/or urgent safety issues
- Does information reported agree with previous knowledge of safety?
- Indicate whether changes have been, or should be, made to clinical trial protocols, informed consent, and/or the investigator's brochure/DCSI, and what the implications are for the trial subjects

Who Should Receive the DSUR?

- The DSUR is first and foremost a regulatory document
- An Executive Summary of the DSUR is recommended for other pertinent stakeholders: Ethics Review Committees (ERCs), DSMBs, Investigators
- A complete DSUR could be provided to DSMBs and to ERCs if requested
- Proprietary information may be redacted

What the DSUR is NOT:

- An evaluation of the benefit-risk relationship for the product
- An interim integrated safety summary (ISS) as submitted for marketing applications
- A repository or discussion of individual adverse experience cases, unless by exception
- A signal detection tool
- An “expert report”

DSUR Format and Contents (1)

- Executive summary
- Introduction
- Worldwide market authorization status
- Update on sponsor or regulatory actions taken for safety reasons
- Changes to Development Core Safety Information (DCSI) or safety sections of Investigator Brochure (IB)

DSUR Format and Contents (2)

- Inventory and status of ongoing and completed interventional clinical trials
- Estimated subject exposure in clinical trials

Inventory and status of ongoing and completed interventional clinical trials

Project name /Formulation: XX /Capsules		*Indication: Hypertension*		*Design Features*		*Enrollment Figures*		*Estimated Pts exposed to drug*
Study ID/ Phase/ Status	**Location**	**Study Title**	**Design Treatment duration**	**Dose & Regimen of Study & control therapy**	**Subject population**	**first patient visit** **planned enrollment**	**Interval/ Cumulative enrollment**	**Interval/ Cumulative patient exposure per treatment arm**
XX-2476 Phase 2 completed	**UK, DE, FR**	**Assessment of safety and efficacy in patients with severe HTN**	**randomized double blind, parallel, placebo controlled** **4 weeks**	**XX: 30 mg** **Placebo**	**Both sexes** **Age: 18-60** **severe HTN**	**01 Jun 2004** **222**	**64/222**	**XX 30mg: 32/111** **Placebo: 32/111**
XX-2666 Phase 3 ongoing	**UK**	**Long-term study in elderly patients with moderate HTN**	**Open-label** **2 years**	**XX: 15 mg** **XX: 30 mg**	**Both sexes** **Age: >60** **Creatinine > 1.5**	**01 March 2005** **300**	**42/112**	**XX 15mg: 21/56** **XX 30mg: 21/56**
Total						**522**	**106/334**	**XX 15mg: 21/56** **XX 30mg: 53/167** **Placebo: 32/111**

DSUR Format and Contents (3)

- Presentation of safety data from clinical trials
  - Sources of data
  - General considerations
  - Line listings: SUSARs filed during the period
  - Summary tabulations (cumulative and interval, including all SAEs irrespective of labeling and causality)
- Synopsis of significant findings from interventional trials
- Observational and epidemiological studies (including registries)

DSUR Format and Contents (4)

- Targeted new interventional safety studies
- Literature sources
- Safety Data from Other Sources
  - Lack of efficacy affecting safety of the trial population
  - Significant manufacturing and quality issues
  - Significant findings from non-clinical sources

DSUR Format and Contents (5)

- Late breaking information
- Overall safety evaluation
- Summary of important risks and missing information
- Actions recommended or taken
- Conclusions
- Appendices

Other Issues to be Covered in the CIOMS VII Report

- Handling drug-drug, drug-device combinations
- Contractual relationships (licensing agreements, e.g.)
- Details on types of data and presentation
- Model DSUR and fictitious samples
- What about Independent investigators and the DSUR?
- Relationship to and transition to the PSUR

CIOMS VII: Vision for Change

- Align the DSUR format and content with that of the established outline of the PSUR
- Create a single, integrated model that incorporates “DSUR-material” that would not ordinarily appear in a “pure” PSUR (and vice versa)
- Analogy: DCSI evolving into the CCSI – a logical, sequential process
- Structure it so independent pre- and post-approval reviewers can access and focus on their material